REMARKS/ARGUMENTS

Claims 10, 19-36, 41 and 42 have been previously withdrawn from consideration as being drawn to a non-elected invention and species. Claims 37, 39 and 40 have been previously canceled and claims 43 - 45 have been previously presented. Claims 1, 3, 4, 17 and 18 are currently amended.

Claims 1, 3, 4, 17 and 18 have been amended to remove "corticosteroids, Cox-2 inhibitors, TNFα blockers or antagonists" from sub part (d) of the claim. Support for the claim may be found on page 20, lines 16-28 and in the paragraph that bridges pages 22 and 23 of the specification.

Applicants wish to bring previously presented (10/13/2005 response) claim 45 to the Examiner's attention. This claim appears to have been inadvertently left out of the January 11, 2006 Office Action.

35 USC 112 Rejection

Claims 1-9, 11-18 and 38 are rejected under 35 USC 112, second paragraph, as being indefinite in its recitation of "consisting of administering "....TNFα blockers or antagonists..." which the Examiner contends makes the claim appear to be open and closed at the same time with respect to type and nature of agents that are administered for inhibiting cell-mediated immune responses or treating an immune system disease. The Applicants respectfully disagree.

The claimed invention is directed to the use of the following three agents to inhibit a cell mediated immune response, treat an immune system disease or inhibit transplant rejections: a first agent that blocks a CD28/CTLA4/B7-mediated signal e.g., soluble CTLA4, L104EA29YIg, 2) a second agent that blocks a CD40/CD154-mediated signal e.g., anti CD 154 antibody, 3) a third agent that blocks an adhesion molecule-mediated interaction e.g., anti-LFA-1 antibody and 4) with or without (optionally) at least one of the agents from a group consisting of cyclophosphamide, FK506, cyclosporine, prednisone, azathioprine, methotrexate, rapamycine, FTY720, leflunomide, mizoribine, mycophenolic acid, 15-deosyspergualine, hydroxychloroquine, sulphasalazopryine, mycophenolate mofetil, and gold salts. The agent listing in sub-part (d) has been amended as described above to consist of specific agents. Consequently, one knowledgeable in the art would know that the claimed invention consists of agent (a), agent (b), agent (c) and at least one agent from (d) or without an agent from (d). Applicants believe that the amended claims have been clarified.

35 USC 102(e) Rejection

Claims 1-7, 9, 12-18 and 37-40 are rejected under 35 USC 102(e) as being anticipated by Digan et al. (US 2002/014200 A1). The claims have been amended to limit "the group consisting of" in sub-part (d) to specific agents non-inclusive of the immunotoxins described in Digan et al. The claimed invention consists of a combination of 3 agents with or without a fourth agent. None of the agents are immunotoxins as described in Digan et al. Consequently, when Digan et al teaches the administration of their immunotoxins either alone or in combination with other pharmaceutical agents to treat transplant rejection, it does not read on the currently claimed methods due to the lack of the primary agent, their immunotoxin. Further, the mere listing of a large group of agents that could be administered in combination with their immunotoxin does not suggest that just any combination of these agents without the immunotoxin would be appropriate for the treatment of transplant rejection.

35 USC 103(a) Rejections

Claims 1-9, 12-18 and 37-40 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US2003/0072754) and Kirk et al. (US2002/0119150) and in further view of Dana et al. (US 2003/0027744). Applicants respectfully disagree.

The Applicants wish to thank the Examiner for the full citation to Dana et al. (US 2003/0027744). Upon review of the Dana et al reference, the Applicants discovered that the Dana et al reference appears to have been filed (April 18, 2002) and published (February 6, 2003) well after the effective filing date (June 8, 2001) of the instant application. Consequently, the Applicants request that the Dana et al reference be removed from the rejection argument since it can not be read as prior art.

Claims 6, 8 and 11 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754), Kirk et al. (US 2002/0119150) and Dana et al. (US 2003/0027744) as applied to claims 1-9, 12-18 and 38 above and further in view of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of

CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies as acknowledged on pages 15-16 of the instant specification and cited in published references. Applicants respectfully disagree.

The Dana et al reference appears to have been filed (April 18, 2002) and published (February 6, 2003) well after the effective filing date (June 8, 2001) of the instant application. Consequently, the Applicants request that the Dana et al reference be removed from the rejection argument since it can not be read as prior art.

Claims 1-9, 11-18 and 38 are rejected under 35 USC 103(a) as being unpatentable over Digan et al.(US 2002/014200 A1) in view of Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456) and known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies as acknowledged on pages 15-16 of the instant specification and cited in published references. Applicants respectfully disagree.

As pointed out above, the Applicants have addressed the Examiner's concern that the method claims appear to be open and closed with respect to the type and nature of agents that are administered by limiting the group consisting of in sub-part (d) to specific agents. Further, as discussed above, the mere listing of a large group of agents that could be administered in combination with their immunotoxin in Digan does not suggest that just any combination of these agents without the immunotoxin would be appropriate for the treatment of transplant rejection. The fact that the reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the agents listed in Digan without the immunotoxin described in Digan.

Claims 6 and 43-44 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150), as applied to claims 1-9, 12-18 and 38 above and further in view of Peach et al. (US2003/0219863).

While one of ordinary skill in the art might have been motivated by Peach et al. to substitute L104EA29YIg for CTLA4Ig in a combination therapy taught by Blazer et al,. they would have been motivated to administer a double combination to take advantage of the higher avidity of

L104EA29YIg over CTLA4. A double combination that was more effective with less potential for toxicity would be the teachings from this grouping of references.

Applicants respectfully request the Examiner to reconsider and withdraw the above rejections. The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment. The Examiner is invited to contact the undersigned if there are any questions relating to the prosecution of this application.

Respectfully submitted,

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